Role of p38 MAPK and Tie2 in the Pathogenesis of MDS and Their Inhibition by Dual Inhibitor ARRY-614

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Abstract #2825

Introduction

ARRY-614 Inhibits p38 Phosphorylation in Bone Marrow Hematopoietic Lineages is Decreased

• The molecular mechanisms underlying MDS pathophysiology are unclear, but emerging data support a role for both p38 mitogen activated kinase (p38) and TEK tyrosine kinase, endothelial (Tie2). p38 is a major regulator of cellular response to stress, and in MDS, the abnormal cell cycle leads to increased apoptosis of progenitors and subsequent peripheral cytopenias. p38 is over-expressed in MDS bone marrow and thought to contribute to this process.

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ARRY-614 is a dual inhibitor of p38 and Tie2 that has demonstrated the ability to improve blood counts in 1 or more lineages in patients with IPSS Low/Intermediate(Int)-1 risk MDS.

Summary of ARRy-614-111 Dose Escalation and Expansion in IPSS Low/MDS Phase 1 Study

<table>
<thead>
<tr>
<th>Dose Level (mg)</th>
<th>n</th>
<th>Cohort</th>
<th>PFS % (at screening)</th>
<th>MDS Pathology %</th>
<th>Total Daily Dose (mg)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>400 (n=15)</td>
<td></td>
<td></td>
<td>72 (47 – 84)</td>
<td>40%</td>
<td>400 (n=15)</td>
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<tr>
<td>600 (n=10)</td>
<td></td>
<td></td>
<td>33%</td>
<td>40%</td>
<td>600 (n=10)</td>
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</tr>
<tr>
<td>900 (n=3)</td>
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<td>20%</td>
<td>50%</td>
<td>900 (n=3)</td>
<td></td>
</tr>
<tr>
<td>1200 (n=16)</td>
<td></td>
<td></td>
<td>38%</td>
<td>30%</td>
<td>1200 (n=16)</td>
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</tr>
</tbody>
</table>

**Note:** Includes all patients who had PK assessments on Day 15, QD Dosing only

**Includes all patients who had a fresh Baseline and post-dose bone marrow biopsy sample, ARRY-614-111 only

**Dose escalation ongoing (data up to 114/2012), protocol allowed additional patients at tolerated dose levels

**Patients included in PK and PD analyses

<table>
<thead>
<tr>
<th>Study Formulation</th>
<th>MDS Patients Included</th>
<th>Patients Included</th>
<th>PD/Tables</th>
<th>PK/Tables</th>
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<tbody>
<tr>
<td>ARRy-614-111</td>
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<td>ARRy-614-112</td>
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</tbody>
</table>

**ARY-614 inhibits p38 phosphorylation in bone marrow of MDS patients.

ARY-614 Inhibits Cleaved Caspase-3 (CC3) in Patient Bone Marrow

CC3 Not Elevated in Healthy, Age-Comparable Bone Marrow

• MDS patients have aberrant p38 activation and increased apoptosis as measured by elevations in CC3 at Baseline

• ARRY-614 treatment decreases p38 and CC3 in the bone marrow of MDS patients

ARRY-614 Inhibits p38 Phosphorylation in Bone Marrow

ARY-614 Inhibits Phosphorylation of p38 and Tie2 at Relevant Human Plasma Concentrations

Experiment Design/Methods for Target Inhibition

• CD34+ positive cells from pooled human cord blood (All Cells) were separated by multi-parameter flow cytometry using cell surface markers into HSC-2, CMP and GMP populations.

• Expression of Tie2 pathway constituents were determined by quantitative PCR

• Data analyzed by two-tailed, Student’s T-test (*p<0.05)

Experimental Design/Methods

• HSC-2, CMP and GMP populations were cultured with or without ARRY-614 (82.1%) or Tie2 (102.8%).

• Expression of Tie2 pathway constituents were determined by quantitative PCR

• CD34+ positive cells from pooled human cord blood (All Cells) were separated by multi-parameter flow cytometry using cell surface markers into HSC-2, CMP and GMP populations.

• Data analyzed by two-tailed, Student’s T-test (*p<0.05)

ERY-614 Formulated Capsule Improves Bioavailability and Estimated Target Coverage

<table>
<thead>
<tr>
<th>Dose Level (mg)</th>
<th>n</th>
<th>Total Daily Dose (mg)</th>
<th>n</th>
<th>Dose Level (mg)</th>
<th>n</th>
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**ERY-614 formulative capsule increases bioavailability and achieves a higher Cmax compared to powder-in-capsule

**Formulated capsule enhances target coverage for p38 and Tie2

**800 mg QD dosing continuously maintains plasma concentrations above p38 IC50

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